Early detection of prostate cancer: the EAU versus the AUA recommendations

D. Mortier, MD[1], H. van Poppel, MD, PhD[1]

To present a comparison between the recommendations for early detection of prostate cancer in men without evidence of prostate cancer related symptoms, as proposed by the European Association of Urology and the American Urological Association.

Prostate-specific antigen screening for prostate cancer has been and still is one of the most controversial issues in medicine. Recent guideline statements and recommendations have led to further confusion and controversy regarding the use of prostate-specific antigen testing for the early detection of prostate cancer.

In this text we try to summarise the different points of view of both societies and the evidence they are based upon.

(Belg J Med Oncol 2015;9(5):179-82)

Introduction

In the industrialised world, prostate cancer (PCa) mortality varies widely from country to country. The factors that determine the risk of developing clinical PCa are not well known. There are three well-established risk factors for PCa: increasing age, ethnic origin and heredity.[1-3]

The purpose of screening is to reduce PCa specific and overall mortality and to improve men's future quality of life by the detection of the disease in a curable stage and thus to prevent the occurrence of locally advanced or metastatic disease.[4]

The recently updated European Association of Urology (EAU) guidelines do not recommend widespread mass screening for PCa but do strongly recommend early detection in well-informed men. The American Urological Association (AUA) emphasises shared decision making, which is a vague concept and difficult to achieve in real life.

Statements

The AUA has recently released new guidelines for the early detection of PCa.[5] In brief, the new guideline (1) does not recommend prostate-specific antigen (PSA) screening in men <40 years (yr) of age, (2) does not recommend routine PSA screening in men 40-54 yr of age at average risk, (3) does recommend shared decision making for men 55-69 yr of age, (4) does recommend a screening interval ≥2 yr, and (5) does not recommend PSA screening in men >70 yr of age or in men with a life expectancy of <10-15 yr.

The EAU has different recommendations for the early detection of PCa.[6] The EAU states that (1) early detection of PCa reduces PCa-related mortality, (2) early detection of PCa reduces the risk of being diagnosed and developing advanced and metastatic PCa, (3) a baseline PSA should be obtained at 40-45 yr of age, (4) intervals for early detection of PCa should be adapted to the baseline PSA level, (5) PSA screening should be offered

[1]Department of Urology, University Hospital Leuven, Leuven, Belgium.

Please send all correspondence to: D. Mortier, MD, Bergstraat 74, 9270 Laarne, Belgium, tel: +32 473 21 16 48, email: dries.mortier@hotmail.com.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: baseline PSA, guidelines, mortality, prostate cancer, prostate-specific antigen, screening.

to men with a life expectancy of ≥10 yr and (6) multivariable clinical risk-prediction tools need to be integrated into the decision-making process.

Discussion

Men aged <40 yr

The AUA does not recommend PSA screening in men <40 yr of age, which is reasonable as the prevalence of PCa in this age group is extremely low and none of the prospective randomised trials on PCa screening involved men <40 yr of age.[7] In this age group there is no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups apply. The EAU doesn't mention this age group, but one could assume that in silence they adopt this notion.

Baseline PSA in men aged 40-54 yr

The AUA does not recommend routine screening in men between ages 40-54 years at average risk. In addition to this statement, the AUA highlights its view that the likelihood of causing harm is high and that any benefit is marginal. It appears to have completely dismissed evidence (and its own previous view), that a baseline PSA in men in this age group is highly predictive of future prostate cancer, metastasis and death. The EAU on the other hand states that a baseline PSA should be obtained at 40-45 yr, as there is ample evidence that a baseline PSA level above the median PSA for this age group is associated with a significantly increased risk of PCa-related mortality and diagnosis of advanced or metastatic disease even 25 yr after the initial PSA was obtained and that this might be a better indicator of PCa development than other clinical risk factors, such as race, family history or suspicious digital rectal examination.[8-12] To conclude, there is considerable value in having a baseline PSA in this age group and it seems as though the AUA has not recognised the evidence to support this.

Men aged 55-69 yr

The AUA does recommend shared decision making for men 55-69 yr of age. The decision to undergo PSA screening involves weighing the benefits of preventing PCa mortality in one man for every thousand men screened over a decade against the known potential harms associated with screening and treatment. The AUA seems to over-emphasise the harms associated with PSA screening. They portray the reduction in PCa mortality as being very minor (1 in 1000). Men should know that when compared with a man who chooses not to have PSA testing in this age group, those who do have regular PSA testing have a 44% reduction in PCa mortality over a 14 yr period. This statement, embraced by the EAU, is derived from the Göteborg randomised population-based PCa screening.

Screening intervals

There is no evidence supporting a specific screening interval. In all the prospective randomised trials on PCa screening, the interval of screening was never a primary objective. The EAU states that the intervals of screening should be adapted to the baseline PSA.[13-17]

In an analysis of 1,703 men aged 55–65 yr with a PSA level ≤1.0 ng/ml who underwent two screening rounds in the Rotterdam section of the ERSPC, only eight PCa cases were diagnosed at eight yr, resulting in an overall PCa detection rate of 0.47%.[13] These data are similar to findings of other groups that reported a PCa detection rate of 0.08% and 0.9% after follow-up of four and 7.6 yr, respectively.[14,16] Based on these data, a screening interval of approximately eight yr seems to be justified in men with a baseline PSA <1.0 ng/ml.

Screening intervals should be 2–4 yr for men with PSA serum concentrations >1.0 mg/l at 45–59 yr of age, whereas it could be up to eight yr in men with PSA serum concentrations below this threshold value.[13,14] Using this approach, it will be possible to reduce the potential harms of screening by targeting a high risk group of men.

The elderly

The EAU states that PSA screening should be offered to men with a life expectancy of ≥10 yr.[18] There is limited evidence of the effect of screening for PCa in elderly men. In the Göteborg randomised screening trial, only 1.28% of men who were last screened at 69 yr of age, were diagnosed with PCa after a median follow-up of 4.8 yr.[19] In another study, the long-term natural history of untreated, low-risk PCa was evaluated.[20] A total of 40.3% progressed to locally advanced disease, and 18% of men progressed to metastatic disease. The mean time until development of metastases and PCa death was 9.2 and 9.5 yr, respectively. 53.5% and 24.1% of patients who were aged ≤70 and >75 yr at the time of diagnosis experienced local progression, respectively, and 24% and 9.2% of the men aged ≤70 and >75 yr died from PCa. The study demonstrates that local progression and death from PCa can develop even in elderly men with organ-confined disease at the time of diagnosis, so early detection and active treatment

Key messages for clinical practice

1. The purpose of screening is to reduce prostate cancer specific and overall mortality.
2. Prostate-specific antigen screening should be offered only if the patient is well-informed.
3. A baseline prostate-specific antigen should be obtained at 40-45 yr of age.
4. Prostate-specific antigen screening should be offered to men with a life expectancy of ≥10 yr.

seems to be justified in men with a long life expectancy independent of chronological age.

The AUA's strong advice not to offer PSA testing in men >70 yr misrepresents the fact that many men in this age group have a long life expectancy and an early diagnosis of prostate cancer may prevent their premature death from this disease. Clearly, not all men in their 70's are the same but following this advice to the letter could deny many men the option of avoiding death from prostate cancer in later life.

To conclude, not age itself but rather comorbidities are the major factor that should be considered when discussing screening or treatment of PCa.

The future

Currently, we know that increasing age, ethnicity, and family history represent established risk factors for diagnosis of PCa. To date, PSA is the single most important parameter for identifying men with an increased risk of PCa and PSA screening results in a significant reduction in PCa related mortality, diagnosis, and development of advanced and metastatic PCa.[21,22] To improve the accuracy of PSA screening, multivariable clinical risk-prediction tools have already been developed (e.g. the PCPT or the ERSPC risk calculator).[23-25] Besides risk calculators, clinical parameters to assess the risk of PCa such as new serum or urinary biomarkers might be used in the future and multiple genetic mutations have been identified that may be implicated in prostate carcinogenesis. However, it is currently unknown how to integrate these discoveries into early detection practices.

Conclusion

Much progress has been made in the last few decades with a 30% reduction in prostate cancer-specific mortality since the introduction of PSA testing.[21,22] And while we accept that this has led to a large amount of over-treatment of less aggressive disease, it is clear that active surveillance is being enthusiastically embraced for appropriate patients. Any return towards the pre-PSA era would likely lead to a reversal in these mortality gains and we would again see many more men presenting with incurable disease.

This continued discussion on whether PSA testing is meaningful, is likely to become redundant in the years to come when better risk stratification with genomic tools and improved imaging will complement the PSA test, rather than relying on it alone.

References

1. Kheirandish P, Chinegwundoh F. Ethnic differences in prostate cancer. Br J Cancer. 2011;105(4):481-5.
2. Jansson KF, Akre O, Garmo H, et al. Concordance of tumour differentiation among brothers with prostate cancer. Eur Urol. 2012;62(4):656-61.
3. Hemminki K. Familial risk and familial survival in prostate cancer. World J Urol. 2012;30(2):143-8.
4. Baum M. Screening for prostate cancer: can we learn from the mistakes of the breast screening experience? Eur Urol. 2013;64:540-1.
5. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. J Urol. 2013;190:419–26.
6. Heidenreich A, Abrahamsson P-A, Artibani W, et al. Early detection of Prostate Cancer: European Association of Urology Recommendation. Eur Urol. 2013;64:347-54.
7. Li J, Djenaba JA, Soman A, et al. Recent trends in prostate cancer incidence by age, cancer stage, and grade, the United States, 2001-2007. Prostate Cancer. 2012;2012: 691380.
8. Loeb S, Roehl KA, Antenor JA, et al. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology. 2006;67:316–20.
9. Fang J, Metter EJ, Landis P, et al. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. Urology. 2001;58:411–6.
10. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA. 1995;273:289–94.
11. Stenman UH, Hakama M, Knekt P, et al. Serum concentrations of prostate-specific antigen and its complex with alpha 1- antichymotrypsin before diagno-

sis of prostate cancer. Lancet. 1994;344:1594–8.
12. Whittemore AS, Lele C, Friedman GD, et al. Prostate-specific antigen as predictor of prostate cancer in black men and white men. J Natl Cancer Inst. 1995;87:354–60.
13. Ito K, Yamamoto T, Ohi M, et al. Possibility of re-screening intervals of more than one year in men with PSA levels of 4.0 ng/ml or less. Prostate. 2003;57:8–13.
14. Roobol MJ, Roobol DW, Schröder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/ml or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology. 2005;65:343–6.
15. van Leeuwen PJ, Roobol MJ, Kranse R, et al. Towards an optimal interval for prostate cancer screening. Eur Urol. 2012;61:171–6.
16. Aus G, Damber JE, Khatami A, et al. Individualized screening interval for prostate cancer based on prostate-specific antigen level: results of a prospective, randomized, population-based study. Arch Intern Med. 2005;165:1857–61.
17. van Leeuwen PJ, Connolly D, Tammela TL, et al. Balancing the harms and benefits of early detection of prostate cancer. Cancer. 2010;116:4857–65.
18. Heidenreich A, Bastian PJ, Bellmunt J, et al. Guidelines on prostate cancer. European Association of Urology Web site. http://www.uroweb.org/guidelines/online-guidelines. Updated 2014.
19. Grenabo Bergdahl A, Holmberg E, Moss S, et al. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. Eur Urol. 2013;64(5):703-9.
20. Popiolek M, Rider JR, Andrén O, et al. Natural history of early, localized prostate cancer: a final report from three decades of follow-up. Eur Urol. 2013;63:428–35.
21. Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med. 2012;366:981–90.
22. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010;11:725–32.
23. Parekh DJ, Ankerst DP, Higgins BA, et al. External validation of the Prostate Cancer Prevention Trial risk calculator in a screened population. Urology. 2006;68:1152–5.
24. Nam RK, Kattan MW, Chin JL, et al. Prospective multi-institutional study evaluating the performance of prostate cancer risk calculators. J Clin Oncol. 2011;29:2959–64.
25. Roobol MJ, Steyerberg EW, Kranse R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. Eur Urol. 2010;57:79–85.